

# **Proposition 65 Maximum Allowable Daily Level (MADL) for Reproductive Toxicity for Arsenic (Inorganic Oxides)**

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## **Office of Environmental Health Hazard Assessment Reproductive and Cancer Hazard Assessment Section**

### **Summary**

The maximum allowable daily level (MADL) for arsenic (inorganic oxides) is **220 µg/day**. This value is applicable to oral, inhalation and dermal routes of exposure and was derived as described below, based on a developmental toxicity study in mice conducted by WIL Research Laboratories (1988).

### **Background**

This report describes the derivation of a maximum allowable daily level (MADL) for arsenic (inorganic oxides), chemicals listed under Proposition 65 as known to the State to cause reproductive toxicity, effective May 1, 1997. For purposes of Proposition 65, arsenic (As) oxides includes arsenate and arsenite salts, arsenic trioxide, arsenic pentoxide, arsenic acid, arsenous acid and other arsenic compounds that dissociate to the oxyanion species. Exposure at a level 1,000 times greater than the MADL is expected to have no observable effect. Procedures for the development of Proposition 65 MADLs are provided in regulation (Title 22, California Code of Regulations [22 CCR], Sections 12801 and 12803).

The Proposition 65 listing of arsenic (inorganic oxides) was based on a finding by the Developmental and Reproductive Toxicant (DART) Identification Committee, the Proposition 65 state's qualified experts for reproductive toxicity, that the chemicals had been clearly shown by scientifically valid testing according to generally accepted principles to cause developmental toxicity. As part of its deliberations, the Committee reviewed the document "Evidence on Developmental and Reproductive Toxicity of Arsenic" (OEHHA, 1996), a comprehensive review of the scientific literature on the adverse reproductive effects of arsenic. This review serves as the primary reference for MADL development.

As defined in regulations, MADLs are derived from No Observable Effect Levels (NOELs) or Lowest Observable Effect Levels (LOELs) (22 CCR Sections 12801 and 12803). The values discussed below are the highest exposure level at which no effect was observed, or the lowest exposure level at which an adverse effect was observed, under the specific conditions of the study in question.

## Study Selection

Relevant data on the reproductive toxicity of inorganic arsenic have been summarized in the document, "Evidence on Developmental and Reproductive Toxicity of Arsenic" (OEHHA 1996). In addition, animal studies published from 1996 to 2001 and recent studies in human populations were identified through literature searches and reviewed. These studies are identified in the Appendix.

The NOEL is based on the most sensitive study deemed to be of sufficient quality (22 CCR Section 12803(a)(4)). Sufficient exposure information was not provided in humans studies to determine a NOEL. Three studies using repeated oral doses of arsenic oxides during gestation (WIL Research Laboratories, 1988; Hazelton Laboratories 1990; Holson et al., 2000) gave similar values for no effect levels (2.6, 3.8 and 4.0 mg As/kg/day, respectively). These three studies demonstrated fetal mortality and developmental delay at the LOEL (13, 13 and 8 mg As/kg/day, respectively).

species	Type of study	Form of arsenic	NOEL	LOEL	reference
			mg As/kg/day		
mouse	Multigeneration	Arsenic acid As (V)	2.6	13	Hazelton Laboratories, 1990
mouse	Developmental toxicology	Arsenic acid As (V)	3.8	13	WIL Research Laboratories, 1988
rat	Developmental toxicology	Arsenic trioxide (As III)	3.8	7.6	Holson et al., 2000

Greater uncertainty accompanies the estimate of effective arsenic intake in the Hazelton Laboratories (1990) mouse study (2.6 mg/kg/day) because arsenic was administered over a longer period of time during which weight and food intake varied. Thus a 3.8 mg/kg dose was selected as the NOEL for MADL development (WIL Research Laboratories, 1988; Holson et al., 2000).

## MADL Calculation

The NOEL is the highest dose level which results in no observable reproductive effect, expressed in milligrams of chemical per kilogram of bodyweight per day (22 CCR Section 12803(a)(1)). The NOEL is converted to a milligram per day dose level by multiplying the assumed human body weight by the NOEL (22 CCR Section 12803(b)). For developmental toxicity, the assumed body weight of the pregnant woman is 58 kg.

$$\text{NOEL} = 3.8 \text{ mg As/kg-day} \times 58 \text{ kg} = 220 \text{ mg As/day}$$

The MADL is derived by dividing the NOEL by one thousand (1,000) to arrive at the maximum allowable dose level (22 CCR Section 12801(b)(1)). Thus, the adjusted NOEL was divided by 1,000 to obtain the MADL.

$$\text{MADL} = 220 \text{ mg As/day} \div 1000 = \mathbf{220 \text{ } \mu\text{g As/day}}$$

In addition to oral exposure, inorganic arsenic can also be absorbed through the lung and skin. This MADL is assumed to hold for inhalation and dermal routes in the absence of sufficient data for developing a separate MADL for inhalation and dermal exposure.

## References

Hazelton Laboratories of America (1990). Two generation dietary reproduction study with arsenic acid in mice. Report #HLA 6120-138, Hazelton Laboratories, Inc., Madison, WI.

Holson JF, Stump DG, Clevidence KJ, Knapp JF, Farr CH. (2000). Evaluation of the prenatal developmental toxicity of orally administered arsenic trioxide in rats. *Food Chem Toxicol* **38**: 459-466.

OEHHA (1996). Office of Environmental Health Hazard Assessment. Evidence on Developmental and Reproductive Toxicity of Arsenic. Reproductive and Cancer Hazard Assessment Section, OEHHA, California Environmental Protection Agency. September 1996. Available at URL: [http://www.oehha.ca.gov/prop65/CRNR\\_notices/hid.html](http://www.oehha.ca.gov/prop65/CRNR_notices/hid.html).

WIL Research Laboratories (1988). A teratology study in mice with arsenic acid (75%). WIL Research Laboratories, Inc., Ashland, OH.

## Appendix

### **Additional references reviewed since publication of “Evidence on Developmental and Reproductive Toxicity of Arsenic” (OEHHA 1996)**

The following studies were identified in a literature search conducted to identify relevant literature published subsequent to the development of the OEHHA (1996) review. They were reviewed along with the studies in OEHHA (1996) to evaluate the most appropriate basis for derivation of a MADL.

Ahmad S, Kitchin KT, Cullen WR. (2000). Arsenic species that cause release of iron from ferritin and generation of activated oxygen. *Arch Biochem Biophys* **382**(2): 195-202.

Calderon J, Navarro ME, Jimenez-Capdeville ME, Santos-Diaz MA, Golden A, Rodriguez-Leyva I, Borja-Aburto V, Diaz-Barriga F. (2001). Exposure to arsenic and lead and neuropsychological development in Mexican children. *Environ Res* **85**(2): 69-76.

Chen NY, Ma WY, Huang C, Ding M, Dong Z. (2000). Activation of PKC is required for arsenite-induced signal transduction. *J Environ Pathol Toxicol Oncol* **19**(3): 297-305.

DeSesso JM, Jacobson CF, Scialli AR, Farr CH, Holson JF. (1998). An assessment of the developmental toxicity of inorganic arsenic. *Reprod Toxicol* **12**(4):385-433.

Gerr F, Letz R, Ryan PB, Green RC. (2000). Neurological effects of environmental exposure to arsenic in dust and soil among humans. *Neurotoxicology* **21**(4): 475-87.

Holson JF, DeSesso JM, Jacobson CF, Farr CH. (2000). Appropriate use of animal models in the assessment of risk during prenatal development: an illustration using inorganic arsenic. *Teratology* **62**:51-71.

Holson JF, Stump DG, Clevidence KJ, Knapp JF, Farr CH. (May 2000). Evaluation of the prenatal developmental toxicity of orally administered arsenic trioxide in rats. *Food Chem Toxicol* **38**(5): 459-466.

Holson JF, Stump DG, Ulrich CE, Farr CH. (1999). Absence of prenatal developmental toxicity from inhaled arsenic trioxide in rats. *Toxicol Sci* **51**:87-97.

Hopenhayn-Rich C, Browning SR, Hertz-Picciotto I, Ferreccio C, Peralta, C, Gibb H. (2000). Chronic arsenic exposure and risk of infant mortality in two areas of Chile. *Environ Health Perspect* **108**:667-673.

Ihrig MM, Shalat SL, Baynes C. (1998). A hospital-based case-control study of stillbirths and environmental exposure to arsenic using an atmospheric dispersion model linked to a geographical information system. *Epidemiology* **9**:290-294.

Infante-Rivard C, Olson E, Jacques L, Ayotte P. (2001). Drinking water contaminants and childhood leukemia. *Epidemiology* **12**(1): 13-9.

Jacobson CF, Stump DG, Nemec MD, Holson JF, DeSesso JM. (1999). Appropriate exposure routes and doses in studies designed to assess developmental toxicity: a case study of inorganic arsenic. *Int J Toxicol* **18**:361-368.

Karagas MR, Tosteson TD, Blum J, Klaue B, Weiss JE, Stannard V, Spate V, Morris JS. (2000). Measurement of low levels of arsenic exposure: a comparison of water and toenail concentrations. *Am J Epidemiol* **152**:84-90.

Nemec MD, Holson JF, Farr CH, Hood RD. (1998). Developmental toxicity assessment of arsenic acid in mice and rabbits. *Reprod Toxicol* **12**:647-658.

Ng JC, Kratzmann SM, Qi L, Crawley H, Chiswell B, Moore MR. (1998). Speciation and absolute bioavailability: risk assessment of arsenic-contaminated sites in a residential suburb in Canberra. *Analyst* **123**:889-892.

Ruan Y, Peterson MH, Wauson EM, Waes JG, Finnell RH, Vorce RL. (2000). Folic acid protects SWV/Fnn embryo fibroblasts against arsenic toxicity. *Toxicol Lett* **117**(3): 129-37.

Stump DG, Holson JF, Fleeman TL, Nemec MD, Farr CH. (1999). Comparative effects of single intraperitoneal or oral doses of sodium arsenate or arsenic trioxide during in utero development. *Teratology* **60**:283-291.

Waalkes MP, Keefer LK, Diwan BA. (2000). Induction of proliferative lesions of the uterus, testes, and liver in swiss mice given repeated injections of sodium arsenate: possible estrogenic mode of action. *Toxicol Appl Pharmacol* **166**(1): 24-35.